COMPOSITIONS AND METHODS FOR TARGETING A VIRAL INFECTION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 62/711,143 filed Jul. 27, 2018, the contents of which is incorporated herein by reference in its entirety.

GOVERNMENT SUPPORT

[0002] This invention was made with Government support under Grant numbers AI129721, AI112489, AI141002, AI106488, AI127193 awarded by the National Institutes of Health. The Government has certain rights in the invention.

FIELD OF THE INVENTION

[0003] The present disclosure relates to the treatment of a viral infection.

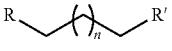
BACKGROUND

[0004] Development of anti-Human Immunodeficiency Virus-1 (HIV-1) strategies remains a global health priority as acquired immunodeficiency deficiency syndrome (AIDS) if often fatal. Although it is generally accepted that an effective vaccine is one way to eradicate this devastating disease, currently there are no promising vaccine candidates on the horizon. In developed countries, combination antiretroviral therapy (cART) has transformed this once fatal illness into a manageable chronic condition. The latest cART regimen uses several classes of antiviral therapeutics, including nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), co-receptor inhibitors (CRIs) and integrase inhibitors (INIs). A typical therapy requires a combination of three or more drugs from at least two classes. Drug resistance, severe side effects and difficulties in patient compliance all call for additional drugs and drug targets. The first of its kind fusion inhibitor approved by FDA is Enfuvirtide, a 36-residue peptide derived from gp41. Enfuvirtide is rarely used, however, because of its numerous disadvantages, and it will be necessary to develop next-generation of fusion inhibitors to overcome these limitations. Described herein are small-molecule inhibitors against a novel target, the membrane proximal external region (MPER) of HIV-1 envelope (Env) useful in preventing and/or treating viral infections (e.g., HIV infections).

SUMMARY OF THE INVENTION

[0005] The compounds, or compositions or pharmaceutical compositions thereof, and methods described herein are related, in part, to the discovery of small-molecule fusion inhibitors that target the membrane proximal external region (MPER) of HIV-1 envelope (Env) spikes. Accordingly, one aspect of the invention described herein provides a compound of Formula (I):

FORMULA (I)



[0006] and pharmaceutically acceptable salts thereof,

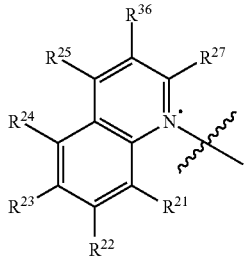
[0007] wherein:

[0008] n is an integer from 3 to 14;

[0009] R and R' are independently selected from the group consisting of:

[0010] (i) Formula (II):

FORMULA (II)



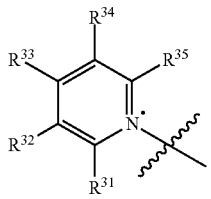
[0011] wherein:

[0012] R^{11}, R^{12}, R^{13}, and R^{15} are independently selected from the group consisting of H, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, carbonyl, carboxy, halogen, nitro, azido, cyano thiol, thioalkoxy, thiocarbonyl, sulfinyl, sulfonyl, thiocarbonyl, cyclyl, heterocylcyl, aryl and heteroaryl; and

[0013] R^{16} and R^{17} are independently selected from the group consisting of H, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, acyl, halogen, nitro, cyano thiol, thioalkoxy, thiocarbonyl, sulfinyl, sulfonyl, thiocarbonyl, cyclyl, heterocylcyl, aryl and heteroaryl, or R^{26} and R^{27}, together with the carbon atoms they are attached to, form a 5-8 membered cyclyl, heterocyclyl, aryl or heteryaryl, each of which can be optionally substituted with 1, 2, 3, or more independently selected substituents;

[0014] (ii) Formula (III):

FORMULA (III)



[0015] wherein:

[0016] R^{31}, R^{32} and R^{33} are independently selected from the group consisting of H, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, carbonyl, carboxy, halogen, nitro, azido, cyano thiol, thioalkoxy, thiocarbonyl, sulfinyl, sulfonyl, thiocarbonyl, cyclyl, heterocylcyl, aryl and heteroaryl; and

[0017] R^{34} and R^{135} are independently selected from the group consisting of H, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, acyl, halogen, nitro, cyano thiol, thioalkoxy, thiocarbonyl, sulfinyl, sulfonyl, thiocarbonyl, cyclyl, heterocylcyl, aryl and heteroaryl, or R^{34} and R^{35}, together with the carbon atoms they are attached to, form a 5-8 membered cyclyl, heterocyclyl, aryl or heteryaryl, each of